Regulation of the Pharmaceutical Industry

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I. Technological Background and Objectives of Regulation

The pharmaceutical industry is characterized by unusually high costs of R&D. The US research-based industry invests about 17 percent of sales in R&D, and the R&D cost of bringing a new compound to market is estimated at $802m. (DiMasi et al. 2003). Reflecting this R&D intensity, pharmaceutical products offer significant health benefits but also entail significant risks. These risks and benefits are non-obvious, can differ across patients, and can only be known with accumulated experience in large patient populations. A major objective of regulation in all industrialized countries is therefore to require that new compounds provide evidence and meet acceptable standards of risks, benefits and manufacturing quality as a condition of market access, with prompt reporting of post-launch adverse events. The main initial focus of regulation since the 1930s was safety, and this has reemerged recently as a critical issue. Since the 1960s most countries also require evidence of efficacy, manufacturing quality, and regulate promotion and advertising to physicians and to consumers.

The economic rationale for these requirements is the public good nature of information gathering and evaluation – that a regulatory agency that has both medical and statistical expertise can more accurately and efficiently monitor and evaluate the evidence from clinical trials than can individual physicians or patients. However, regulation that requires extensive pre-launch clinical trial data on risks and benefits increases the R&D costs incurred by firms, increases delay in launch new medicines, and may reduce the number of drugs developed and the extent of competition within therapy groups. The size and duration of clinical trials required to detect remote risks or cumulative risks from long term therapies can be large. Thus recent efforts are shifting towards how regulators can optimally integrate evidence from pre-approval clinical trials with post-approval observational experience. Regulation of promotional messages – both detailing to physicians and direct-to-consumer advertising to patients -- is also under scrutiny. In the US, in addition to this statutory regulation through the Food and Drug Administration (FDA), the pharmaceutical industry increasingly faces indirect regulation through tort liability.

A second key characteristic of the pharmaceutical industry is that the high costs of R&D imply a cost structure with high, globally joint fixed costs and low marginal costs of production. Patents are therefore essential to enable innovator firms to recoup their R&D investments. However, patents raised many unresolved issues. Charges of excessive prices are used as a rationale for price regulation in some countries. The regulatory criteria and timing of post-patent entry of generics remain contested even for traditional chemical compounds. More complex and yet to be resolved by regulatory agencies are the conditions for authorizing “biogenerics”, that is, authorized generic substitutes of large molecule, biotechnology products such as proteins, monoclonal antibodies etc. As the number and utilization of these

expensive biologics expands, so does concern to establish a low-cost regulatory path for approval of generic biologics, in order to stimulate post-patent price competition. Finally, the global nature of pharmaceutical products is raising important international questions related to patents. Patents are traditionally national in scope. Proposals in the US to legalize drug importation by third parties, such as wholesalers and pharmacies, undermine the traditional right of patent holders to bar unauthorized distribution of the patented product within national boundaries. Moreover, as more developing countries join the WTO and are required to adopt the standard 20 year product patent term, concerns arise over the effects of patents on drug prices and affordability. Appropriate provisions for compulsory licensing of pharmaceuticals remain contested.

A third characteristic of the pharmaceutical industry is the dominant role of third party payment through social and private health insurance schemes. Like any insurance, third party payment for drugs creates moral hazard, with incentives for consumers to overuse and/or use unnecessarily expensive drugs. In addition, by making demand less elastic, insurance creates incentives for firms to charge higher prices than they would in the absence of insurance. In response to these effects, since the 1980s government-run health systems in most countries have adopted elaborate regulatory systems to control pharmaceutical expenditures, through regulation of manufacturer prices or reimbursement, limits on rate of return on capital, on total drug spending or on company revenues. The controls adopted by public insurers have significant effects on demand for pharmaceuticals, on the nature of competition and hence on profitability,incentives for R&D and the supply of new medicines.

As most pharmaceuticals are potentially global products, the effects of price controls on R&D reflect the interaction and aggregate effects of policies adopted by countries that individually face perverse incentives. Each country faces a short run incentive to adopt regulatory policies that best control its current pharmaceutical prices, while free riding on others to pay for the joint costs of R&D. But at the limit, if each country drivesits prices down to country-specific marginal cost, R&D cannot be sustained. The global nature of pharmaceuticals and the long R&D lead times – 12-14 years from drug discovery to product approval, on average – make the incentives for short run free riding by individual countries particularly acute. While there is widespread consensus in support of differential pricing between the richest and poorest nations, no consensus exists on appropriate price levels for these countries or between high and middle-income countries. In practice, the ability of pharmaceutical firms to price discriminate is diminishing as more countries adopt national price regulatory policies that reference prices in other countries and/or legalize drug importation (also called parallel trade or international exhaustion of patent rights). These cross-national price spillovers in turn create incentives for firms to delay or not launch new drugs in low price markets, if these low prices would undermine potentially higher prices in other markets. Thus the design of each country's regulatory system can affect availability of drugs in other countries through price spillovers in the short run, and through R&D incentives in the long run.

Unlike some other industries, regulation of the pharmaceutical industry has not diminished or undergone fundamental changes over recent decades, although focus shifts over time between concerns for safety vs. cost and delays. The motivations for regulation of pharmaceuticals -- imperfect and/or asymmetric information for drug approval regulation, patents and insurance-related moral hazard for price and profit regulation – remain and have, if anything, increased over time. Nevertheless, regulatory trends over time within the US and cross-national differences provide a wealth of useful experience from which some lessons can be learned. This review will focus primarily on US issues and evidence, reflecting the dominance of US-based literature. Moreover, US regulatory policy has a disproportionately large effect on the industry, because the US market accounts for almost fifty percent of global pharmaceutical revenues. However, we draw extensively on experience from other countries for evidence on price and reimbursement regulation, cross-national spillover effects and access to pharmaceuticals in developing countries.

Figure 1: Objectives and Types of Regulation for the Pharmaceutical Industry

Motivations for Regulation	**Types of Regulation**
Imperfect and asymmetric information asymmetry about safety and efficacy	Market access requirements of the FDA or EMEA Regulation of promotion Tort liability
High fixed costs of R&D	Patents and regulation of generic entry (Hatch Waxman) Orphan Drug Act Accelerated approval measures (PDUFA)
Insurance-induced moral hazard	Regulation of prices, reimbursement, profits, expenditure/revenues

II. Overview of Safety and Efficacy Regulation

1. The US

The first comprehensive federal legislation regulating food and drugs in the US was the Pure Food and Drug Act of 1906 (The Wiley Act) which required that product labels and packaging not contain false statements about curative effects, but stopped short of requiring manufacturers to provide evidence to prove safety or efficacy (Palumbo FB 2002). The 1938 Food, Drug and Cosmetics Act (FDCA), which replaced the Wiley Act, required any firm seeking to market a new chemical entity (NCE) to file a new drug application (NDA) to demonstrate that the drug was safe for use as suggested by the proposed labeling. The Food and Drug Administration (FDA) had 180 days to reject the NDA. As new forms of print and radio

advertising had emerged since the Wiley act, the FDCA established jurisdiction over drug advertising, but policing was left to the Federal Trade Commission (FTC) rather than the FDA. This Act also established the requirement that patients obtain a prescription from a physician in order to obtain retail drugs.

The 1962 Kefauver-Harris Amendments to the 1938 FDCA were triggered by the thalidomide tragedy. The drug thalidomide had caused hundreds of birth defects in Europe but was still under review in the US. These Amendments strengthened safety requirements; added the requirement that drugs show proof of efficacy, usually by double blind, randomized controlled trials of the drug relative to placebo; removed the time limit (previously 180 days) within which the FDA could reject an NDA; extended FDA regulation to cover clinical testing and manufacturing; restricted manufacturers' promotion to approved indications; and required that all promotional material must include a summary of side-effects and contraindications. Regulatory oversight of promotional material was ceded back to the FDA from the FTC. Basic requirements for promotional materials were defined, including, that such materials cannot be false or misleading; they must provide a fair balance of risks and benefits; and they must provide a "brief summary" of contraindications, side effects and effectiveness.

The presumption underlying the requirement for proof of efficacy was that imperfect and possibly asymmetric information prevented physicians and consumers from making accurate evaluations, leading to wasted expenditures on ineffective drugs and excessive product differentiation that undermined price competition. However, the extent of the market failure was unknown, and the added requirements clearly added costs for firms (albeit with the intention of reducing potentially larger costs for consumers). Phase III trials to establish efficacy became the most costly and time consuming component of clinical trials which, together with increased regulatory review time, added to delay in the launch of new drugs, leading to foregone benefits for consumers, shorter effective patent life and foregone revenue for firms. Moreover, since some regulatory costs are fixed, independent of potential market size, such regulation raises the expected revenue threshold required to break even on a new drug, leading to higher break-even prices, *ceteris paribus,* and fewer drugs, particularly drugs to treat rare diseases with small potential market size.

Subsequent legislation has addressed several of these cost-increasing effects of the 1962 Amendments. The Orphan Drug Act of 1983 (ODA) significantly increased incentives to invest in orphan diseases (defined as conditions that affect less than 200,000 individuals in the US) by increasing revenues and decreasing costs: drugs that receive orphan status are granted market exclusivity for seven years (that is, competitor compounds will not be approved to treat the same condition) and receive a 50% tax credit for expenses accrued through clinical testing. In addition, orphan drugs may benefit from research grants from the NIH and accelerated or fast track FDA approval (see below). Following the ODA, R&D on orphan diseases has increased significantly. . Between 1979 and 1983, the rate of orphan drug approvals increased

at approximately the same rate as other drugs. However by 1998, there were more than five times as many orphan drugs as in 1979, but fewer than twice as many non-orphan drugs (Lichtenberg ,2003).

To address the loss of effective patent life due to time spent in clinical trials and regulatory review, the 1984 Patent Term Restoration and Competition Act (hereafter the Hatch-Waxman Act) granted innovator firms an extension of patent term for up to five years.[1] However, as a quid pro quo, the 1984 Act expedited post-patent entry by generic manufacturers, by granting them access to the active ingredient before the actual patent expiry (the Bolar exemption), and granting market access with an Accelerated New Drug Application (ANDA) that requires only that generics prove bioequivalence to the originator product, without extensive new trials. Hatch-Waxman conferred a five year maximum data exclusivity period after the innovator's NCE application (three years for other data not submitted in support of an NCE approval), after which generic firms are free to use innovator clinical trial data to prepare their ANDA (the EU allows 10 years of data exclusivity)(Kuhlik 2004). Moreover, Hatch-Waxman grants to the first generic firm to successfully challenge a patent (a paragraph IV filing) a 180 days as the exclusive generic in the market, after the originator's patent expiry.(Kuhlik 2004) In recent years, originator firms have been accused of "evergreening" their drugs by late filing of follow-on patents on minor aspects of the compound; agreements with and litigation challenges to generics; and follow-on products that resemble that original product except for minor changes that nevertheless may suffice for a new patent e.g. single isomer versions. The FTC has taken antitrust enforcement action against some of these practices (related to the 180 day exclusivity and 30-month stay provisions) (FTC, 2002). The 2003 Medicare Modernization Act includes changes to deter these practices, but this remains an unsettled area.

Hatch-Waxman laid the necessary foundation for fast and cheap generic entry immediately after patent expiry in the US. Generics now comprise over 47 percent of prescriptions, compared to 19 percent in 1984 when Hatch Waxman was enacted (FTC, 2002). However, the rapid and comprehensive generic erosion of originator market shares that now occurs also reflects state-level legislation authorizing pharmacies to substitute generics for originator drugs (unless the physician notes "brand required") and insurance reimbursement incentives to pharmacies and patients to accept generics when available. The speed of generic entry and erosion of originator market shares differ significantly across countries, reflecting regulatory differences in market access and reimbursement incentives, in particular, for pharmacies. Empirical evidence related to Hatch-Waxman as well as cross-national differences are discussed below.

[1] The patent term restoration is 0.5 years per 1 year spent in clinical trials and 1-for-1 for years spent in regulatory review.

An important initiative to reduce delay in the FDA review of regulatory filings was the Prescription Drug User Fee Act (PDUFA) of 1993.[2] Under PDUFA, pharmaceutical firms agreed to pay user fees to the FDA to hire more reviewers and hence expedite drug review. The three separate fees that are collected are substantial. [3]Since 1993 over $1.5 billion has been collected; in fiscal year 2004, the $251 million in fees accounted for 53% of total processing costs at the FDA.(FDA 2005(d))

In addition to user fees, the PDUFA created a "priority review" system that classifies New Drug Applications (NDAs) as either "standard review" or "priority review".(Olson 2004) The FDA set target dates for action at 10 months for standard review and 6 months for priority review drugs which are generally intended to address unmet needs. Prior to 1992, the FDA classified drugs into either A,B or C categories, and an AA category was was developed to speed the review of AIDS products.

The 1997 FDA Modernization Act (FDAMA) renewed the priority review system and defined additional measures to not only speed regulatory review but also potentially expedite the entire clinical trial process for novel drugs via 'Fast Track' status.(Olson 2004; FDA 2005(b)) Fast Track status, which is technically independent from 'priority review', is intended to accelerate clinical trials by additional meetings, correspondence and review programs with the FDA. Firms may files for 'fast track' status for a particular drug at any point in the development process, but products only receive designation if they are "intended for the treatment of a serious or life-threatening condition" and "demonstrate the potential to address unmet medical needs for the condition".(FDA 1997; HHS 2004) In addition, "Accelerated Approval" status refers to FDA acceptance of approval on the basis of a surrogate endpoint that " is reasonably likely to predict clinical benefit" rather than a clinical benefit. Accelerated approval is one of the potential review processes for which fast track drugs may qualify. Fast track has reduced overall development times by approximately 2.5 years.(FDA 2003) Evidence on the effects of fast track and priority review on prevalence of post-approval adverse events is discussed below.

FDAMA also initiated significant change in promotion regulation, by permitting companies to inform physicians of potential unapproved ("off-label") uses of drugs through the distribution of peer reviewed journals. It also permitted companies to issue economic analyses to payers. The law is vague in defining the bounds of the scientific evidence required, stating only that the analysis "shall not be

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[2] This has subsequently been renewed twice as part of the Food and Drug Modernization Act (1997) and the Bioterrorism and Preparedness and Response Act of 2002.
Berndt ER, G. A., Philipson J, Strobeck MW (2005). "Industry Funding of the FDA: Effets of PDUFA on Approval Time and Withdrawal Rates." Nature Reviews: Drug Discovery **4**: 545-554.

[3] The fee for review of data related to product approval is $767,400 for applications with new clinical data, $383,700 for supplemental applications or those with no new clinical data (for fiscal year 2006). There is also a fee for each manufacturing facility ($264,000) and an annual fee for the right to market products ($42,130).(FDA 2005(a)) .

considered to be false or misleading…the health care economic information directly relates to an [approved] indication…and is based on competent and reliable scientific evidence."(FDA 1997)

The interpretation of regulations governing direct-to-consumer (DTC) advertising also changed as a result of an FDA Draft Guidance issued in 1997. Previously, product claim advertisements that named both the drug and the condition it treated were required to disclose all the risks and contraindications within the content of the advertisement.(Wilkes, Bell et al. 2000) The 1997 FDA guidance still required firms to present a "fair balance" between risks and benefits and not mislead with false advertising; however, broadcast ads could meet the requirement for full labeling disclosure by providing information on several other sources to obtain the full label, including a toll-free number, an internet site, a print ad or a "see your physician" advice.(GAO 2002) Much of the growth in DTC advertising after the 1997 draft guidance (formalized in 1999) was in television promotion. For example, total DTC spending grew from $266m. in 1994 to $2.47B. in 2000, but the spending on television DTC increased from $36M to $1.57B over the same time period.

Regulation of drug prices in the US has so far been much more limited than in other countries with national health insurance programs. The largest publicly-funded health insurance program in the US, the Medicare program for seniors, does not cover outpatient prescription drugs until the new Part D drug benefit, authorized in the 2003 Medicare Prescription Drug, Improvement and Modernization Act (MMA), is implemented in 2006. Moreover, the MMA specifically stipulates that the drug benefit is to be delivered through private plans and that these private plans, not the federal government, will negotiate drug prices If, as many anticipate, expenditures under this program exceed original projections future legislation could renounce this pledge, thereby making the US government the purchaser for roughly 50 percent of drug spending. Estimates for the Medicare drug benefit have already increased from $404B for 2004-2013 (CBO 2004) to $724B for 2006-2015 (the Administration's estimate (Kaiser Family Foundation 2005(b))).

So far, government drug purchasing in the US is limited to the federal-state Medicaid program and several smaller federal programs. The 1990 Omnibus and Reconciliation Act requires originator drugs to give Medicaid the lower of (a) the "best price" offered to any non-federal purchaser or (b) a 15.1% discount off AMP (average manufacturer price). Additional, "excess-inflation" rebates are required for price increases that exceed the CPI. Theory and evidence suggest that the "best price" constraint reduced discounts for private payers. For 2003, the combined effect of these mandatory discounts resulted in a 31.4% discount for Medicaid, relative to AMP (CBOb, June 2005). Similarly, for the Big Four Federal programs (the Department of Defense, the Department of Veterans Affairs, the Public Health Service and the Coast Guard) the Federal Ceiling Price mandates a discount of 24 percent off non-federal average manufacturing price, plus an excess inflation rebate. In 2003, the average Big Four price was roughly 38 percent below the AMP (CBO 2003a). Thus public purchasers in the US regulate prices by mandatory

discounts off private sector prices. This has resulted in significantly lower averages prices for public programs, while also reducing discounts granted to private plans.

2. International Perspective on Safety and Efficacy Regulation

Following the thalidomide tragedy and the strengthening of safety and efficacy requirements in the US in 1962, the UK tightened safety regulations in 1964 and added efficacy requirements in 1971. Other industrialized countries have adopted similar regulations, although some, such as France and Japan, have less stringent efficacy requirements (Thomas 1996). Each country has its own approval process, although in practice smaller countries frequently simply review and reference approvals through other major agencies such as the US or the UK Medicines Agency.

In 1995 the European Union established the European Medicines Evaluation Agency (EMEA) as a one-stop approach to drug approval for the EU. The EMEA offers two approaches to drug approvalm. The centralized procedure involves review by the EMEA and provides simultaneous approval of the drug in all countries of the EU. Alternatively, a firm can use the mutual recognition approach, seeking approval by one rapporteur country with reciprocity in other EU countries, subject to their review and objection. The EMEA is the required approval route for biotech products and as optional route for other new drugs. National systems remain for products that seek approval in only a few countries.

Since the 1990s the regulatory authorities and the industry in the three major pharmaceutical markets – the US, the EU and Japan – have worked through the International Commission on Harmonization (ICH) to harmonize their regulatory requirements for safety, efficacy and manufacturing quality, in order to reduce the duplication, expense and delay involved if companies must submit different requirements to each authority. As a result of the harmonization measures, companies can to a significant degree compile a single dossier for submission to the EMEA, the US FDA and Japan, although some important differences remain and each agency still makes its own evaluation based on their own risk-benefit trade-off. For example, the EMEA typically requires trials of new drugs relative to current treatment whereas the FDA more often uses a placebo comparator, except where use of placebo would imply unethical treatment of patients. Japan still requires some country-specific trials.

User fee programs have been adopted by the EMEA and the UK Medicines Agency, to expedite review. As a result of harmonization and other measures, differences in market approval requirements are no longer a major source of difference in timing of drug launch between the US and “free pricing” countries in the EU, notably the UK and Germany (until 2004).

Larger differences remain in the approval process for generics. Measures similar to the US Hatch Waxman provisions have been proposed for the EU but so far have not been adopted by the EMEA or by all countries' regulatory agencies.

More problematic is the appropriate regulatory agency and standards for drugs intended primarily for use in developing countries. Since disease incidence, competing risks, costs and benefits of treatment may be vastly different in these countries, decisions based on FDA or EMEA standards may be inappropriate for these countries. For example, in 1999 Wyeth's pulled its rotavirus vaccine, Rotashield, from the US market due to concern that the risk of severe (but infrequent) intususseption would be unacceptable relative to the vaccine's benefit, given the relatively low risks from rotavirus in the US. Consequently the vaccine became unavailable in developing countries, although the benefit-risk trade-off would have been very different, given the much higher incidence and higher death rates from rotavirus in some countries.

III. Effects of Safety and Efficacy Regulations: Evidence and Issues

1. Costs of Regulation

Much of the early economic analysis of pharmaceutical regulation focused on effects of the 1962 Kefauver-Harris Amendments, in particular, effects of the efficacy requirement on R&D costs, delays in launch of new drugs, and decline in the number of new drug introductions that occurred after the 1962 Amendments, raising questions of causation (for example, Peltzman, 1973; Grabowski et al., 1978; Baily, 1972; Wiggin, 1981).

Number of new drug launches Grabowski, Vernon and Thomas (1978) report that the number of NCEs fell from 233 in the five-year period 1957-1961 to 93 in 1962-1966 and 76 in 1967-1971.(Grabowski, Vernon et al. 1978) Some decline would be consistent with the intent of the legislation, if some of the prior introductions were ineffective. However, the percentage of total ethical drug sales accounted for by new NCEs declined roughly in proportion to the number of drugs, from 20.0 percent in 1957-1961 to 5.5 percent in 1967-1971. This is inconsistent with the argument that only the most insignificant drugs were eliminated. Grabowski et al. also attempt to measure the marginal reduction plausibly attributed to the 1962 US Amendments after controlling for other possible contributing factors, including the depletion of new product opportunities; the thalidomide tragedy that may have made manufacturers and physicians more risk averse, hence reduced demand for new drugs; and pharmacological advances that may have raised R&D costs independent of regulation. They compared trends in NCE discoveries in the US relative to the UK, an appropriate comparator country because of its strong and successful research-based pharmaceutical industry. This is a quasi-natural experiment since the UK did not adopt efficacy requirements until 1971 and its 1963 safety requirements were statistically unrelated to the flow of new discoveries. Grabowski et al.

find that research productivity, defined as number of NCEs per (lagged) R&D expenditure, declined sixfold between 1960-61 and 1966-1970 in the US, compared to a threefold decline in the UK, and that the 1962 US Amendments increased the cost per new NCE by a factor of 2.3. They conclude that these differentials are plausibly attributable to regulation, since the UK would have been equally affected by exogenous changes in scientific opportunities and testing norms and by any thalidomide-related change in demand. In fact, these estimates based on using the UK as a benchmark are probably conservative estimate because regulatory changes in the US, as the largest single pharmaceutical market, would influence incentives for innovative R&D for all firms, regardless of country of domicile, and hence could have contributed to the decline in NCE discoveries in the UK.

R&D Cost per NCE There is little doubt that regulation has contributed to the increase in R&D cost per new drug approved, although the relative contribution of regulation vs. other factors is uncertain. Baily (1972) and Wiggins (1982) concluded that the 1962 Amendments led to a large and significant increase in the R&D cost per new drug approved, but with significant variation across therapeutic categories. More recent evidence shows that the cost of developing new drugs has continued to outpace the CPI. This steady increase in R&D cost per NCE has occurred without explicit new legislation, although less quantifiable changes in regulatory requirements may have occurred. Other possible contributing factors include technology shifts and changes in the types of drugs and diseases at issue, and that growing public demands for safety and efficacy may lead firms to voluntarily undertake more informative trials. DiMasi et al. (2003) found that capitalized cost per approved NCE, measured in present value at launch, grew from $138M in the 1970s to $318M in the 1980s and $802M in the 1990s. Only roughly half of this total cost is out-of-pocket cost, including the cost of failures; the remainder is the capitalization cost (foregone interest or opportunity cost of capital). DiMasi (2001) reports that total cumulative time from drug synthesis to approval increased from 8.1 years for 1963-1969 to 14.2 by 1990-1999.(DiMasi 2001) Number and size of trials has also increased, as has average cost per trial participant.[4]

For certain types of drugs, particularly those used by large populations of relatively healthy subjects, such as vaccines, reluctance to tolerate even remote risks is increasing the size and duration of trials in order to detect very rare adverse events. For example, recent trials for the rotovirus vaccine involve 70,000 patients. In a qualitative survey Coleman et al. (2005) report that vaccine manufacturers attribute vaccine shortages and reduced incentives for discovery, in part, to the high safety standards that are

[4] Boston Consulting Group (BCG, 1993) reports that the mean number of subjects included in NDAs increased from 1576 for 1977–1980, to 1321 for 1981–1984, and 3233 for 1985–1988. A Parexel study of 55% of the approved products between 1998-2001 (n=64) found a mean number of subjects per NDA of 5,621, similar to DiMasi's report for the Center for Study of Drug Development dataset of 5,303.

required by the FDA.[5] On the other hand, regulatory changes (use of biomarkers rather than survival as the endpoints, Fast Track status etc.) to expedite drugs to treat life-threatening diseases with no effective available treatments have no doubt reduced costs and delay, contributing to the dramatic growth in number of cancer drugs in trials in recent years. Other factors such as advances in science and relatively generous reimbursement have also contributed to the proliferation of R&D for these high priority conditions, such that the marginal effects of regulatory changes are hard to identify. However, it seems safe to conclude that, given PDUFA, FDAMA and other measures that have been adopted to expedite trials and review for high priority drugs, the balance has shifted and there is now less concern over undue costs and delay for these drugs, and perhaps more concern over adequate proof of safety and efficacy.

Lags in Launch Several analyses find that the 1962 Amendments increased delay in launch of new drugs in the US relative to other countries (for example, Wardell (1973); Wardell and Lasagna (1975); (Wardell 1973; Wardell WM 1975); Grabowski and Vernon, 1978; Grabowski, 1976; Wiggins, 1981). Grabowski and Vernon (1978) compare introduction dates in the US and the UK for drugs discovered in the US between 1960 and 1974.(Grabowski, Vernon et al. 1978) The proportion of drugs introduced first in the US declined significantly between 1960-1962 and 1972-1974, while the proportion introduced later in the US increasing significantly. The authors conclude that increased regulatory scrutiny in the US caused multinational companies to introduce new products abroad before their US launch. Similarly, Grabowski (1976) finds that many more drugs were introduced first in Europe despite most being discovered in the US or by US-based firms(Grabowski 1976) Dranove and Meltzer (1994) estimate that the average time from a drug's first worldwide patent application to its approval by the FDA rose from 3.5 years in the 1950s to almost 6 years in the 1960s and 14 years in the mid 1980. They also found that, beginning in the 1950s, more important drugs - especially drugs that proved to be successful in the marketplace - have been developed and approved more rapidly than less important drugs. They attribute this differential to actions of drug companies as much as to regulatory priority setting.[6]

However, evidence from the 1990s indicates that the US no longer lags and may lead the major EU markets in number and timing of major new drug launches (Danzon, Wang and Wang, 2004). Given the

[5] On the other hand, Finkelstein (2004) shows regulatory and reimbursement changes that potentially increased expected vaccine revenues stimulated vaccine R&D. Specifically, she examines the effects on vaccine R&D of three plausibly exongeneous shifts in policy (the 1991 CDC recommendation to vaccinate infants against Hep B, the 1993 expansion of Medicare to cover influenza vaccines and the 1986 introduction of the Vaccine Injury Compensation Fund). She finds a lagged increase in vaccine clinical trials after these events (but no increase in early stage patent activity or preclinical trials).
Finkelstein, A. (2004). "Static and dynamic effects of health policy: Evidence from the vaccine industry." Quarterly Journal Of Economics **119**(2): 527-564.

[6] Dranove and Meltzer (1994) used several measures of drug importance, including citations in medical textbooks, in medical journals, and in subsequent patent applications; the extent of worldwide introduction; and US sales. To the extent that these *ex post* measures of importance are noisy measures of *ex ante* forecasts of importance, their estimates of differential delay may be understated.

coordination of standards and similarity of regulatory requirements in the European Medicines Evaluation Agency (EMEA) and the US FDA, differences in launch timing between the US and the EU appear to be driven less by differences in market approval requirements and more by price and reimbursement regulation in the EU, including the fact that price spillovers create incentives for manufacturers to intentionally delay launch in low-price markets. One exception is that although Japan has relatively high launch prices, launch lags have been unusually long in Japan due to its unique market approval requirements, including country-specific trials.

2. Benefits of Safety and Efficacy Regulation

Compared to costs, there are many fewer studies of the benefits to consumers from 1962 Amendments. The only significant attempt to weigh both the benefits and costs of the 1962 Amendments is Peltzman's (1973) study. He attempts to measure the benefit associated with the new efficacy standards by comparing the growth of market shares of drugs launched prior to 1962 to those launched after 1962. The assumption was that new products would capture greater initial market share after 1962 if the Amendments increased the average efficacy of new drugs relative to drugs already on the market. (Peltzman 1973) He concludes that the benefits were minimal and were far outweighed by the costs of regulation, which he estimates as foregone consumer surplus due to the reduced flow of NCEs. These conclusions depend critically on the methods for estimating costs and benefits, which have been questioned (for example, Temin, 1979). In particular, benefits may be understated and costs may be overstated by ascribing the decline in NCEs solely to the regulation. Nevertheless, this is an important study because it offers a theoretical and empirical framework for evaluating the net benefits of the 1962 efficacy requirements.

Recent studies have examined the benefits and costs of the more modest recent changes in regulatory requirements, specifically, the priority review policy introduced by PDUFA in 1992. Undoubtedly, PDUFA expedited the time to market for "priority" drugs. Between 1993 and 2003 the median time to approval declined from 14.9 to 6.7 months, while review times for "standard" products only decreased from 27.2 to 23.1 months.(Okie 2005) Olson uses data from 1990-92 and 1992-95 to examine the difference in the effects of firm characteristics on review times before and after the 1992 PDUFA. She finds that firm characteristics were not associated with review times after 1992, suggesting that the regulatory change helped eliminate firm advantages prior to 1992.(Olson 2000) PDUFA was also subsequently amended to reduce filing fees for smaller firms.

Olson (2004) also attempts to quantify the safety impact of PDUFA and compare the costs of faster approvals to the benefits. She finds that post-launch reports of adverse drug reactions (ADRs) are more likely for drugs that the FDA rates as "priority", after controlling for drug utilization, disease characteristics, patient characteristics, drug review time and year specific effects. Controlling for these

factors, she concludes that there are 60-84% more serious ADRs, 45-72% more ADRs that result in hospitalization and 61-83% more ADRs that result in death due to PDUFA. In order calculate benefits from reduced delay, Olson uses Lichtenberg's estimate of how the increase in the stock of priority review drugs for particular therapeutic categories increased the mean age at death for persons with those conditions.(Lichtenberg 2002) She finds that under the most conservative assumptions (biasing against safety) the safety impact reduces by 8% the total benefit (measured in expected gain in life years) attributed to the faster launch of new drugs due to priority review. This figure increases to 11% if ADRs are under-reported by 30%. Subsequent research has found that ADRs gathered through the FDA post-marketing surveillance mechanisms generally underreport ADRs, but the degree is not well established.(Brewer and Colditz 1999; Bennett, Nebeker et al. 2005) Whereas Olson finds significant negative safety effects of accelerated review, the Government Accounting Office (GAO) found that drug withdrawals rates differed insignificantly between the period before and after the PDUFA.(Berndt ER 2005) This study did not control for other factors that may have influenced drug withdrawals rates.

Neither of these studies estimate the savings to firms from accelerating the R&D process, including reduces the capitalized costs of R&D to firms and increased effective patent life. DiMasi (2002) estimates that a 25 percent reduction in phase length for all phases of clinical trials would reduce the average cost per NCE by $129M, or by 16.1% assuming a base cost of $802M. Since these estimates are based on a random sample of 68 drugs that entered clinical trials between 1983 and 1994, they probably overstate the dollar savings for the types of drugs that receive fast track status, however the percentage effect may be valid.

3. Discussion and Proposals for Change in Regulation of Safety and Efficacy

Despite the reduction in regulatory review times under PDUFA, total R&D time remains high primarily due to duration of Phase III efficacy trials.[7] Concern to reduce duration of clinical trials without sacrificing information has led to growing interest in supplementing pre-launch randomized controlled trials with post-launch observational evidence, from either controlled or uncontrolled studies. Advances in data collection from routine care and in statistical methods for analyzing such data to adjust for possible nonrandom assignment of patients to different treatments offer a potentially rich and relatively cheap source of information that could supplement clinical trial data, in particular, providing larger sample size, particularly on subpopulations, and longer term experience. The Center for Medicare and Medicaid (CMS) is undertaking such studies in order to evaluate effectiveness of alternative treatment regimens for the

[7] DiMasi (2003) p.164-165 suggests that total time from start of human testing to approval for a representative drug is 90.3 in current study vs. 98.9 in prior study. DiMais (2001) p.291 indicates that the duration from start of clinical to end of approval peaked in the late 80s and declined in the post PDUFA era (data up to about 1999).

Medicare Drug Benefit. Integrating such findings with FDA's pre-launch data from RCTs could significantly enhance the information base available for decision-making and potentially affect the relative role of the FDA vs. CMS.

The net benefit to consumers from a shift towards earlier approval of drugs based on biomarkers (such as tumor shrinkage) depends on whether post-launch studies are in fact done to validate effects on true clinical outcomes such as survival. A recent FDA survey found that 65% of the 1,300 post-approval studies assigned to industry have not been started.(FDA 2004)

While public and legislative demand to speed access to new drugs was in vogue in the 1980s and 1990s, more recently there is a revival of demands for raising pre-launch safety requirements. Recent post-launch evidence on risks of some widely used drugs, including the COX-2 inhibitors for arthritis and pain, notably rofecoxib (Vioxx) and valdecoxib (Bextra), and the anti-depressants, have led to a range of proposals to enhance regulatory protection of safety. The FDA's expanded MedWatch program will report adverse events on an FDA website as soon as reported.(Longman 2005; FDA 2005(c)), enabling consumers to draw their own conclusions. In February 2005 the FDA announced plans to establish a Drug Safety Oversight Board (DSOB) that will coordinate with outside experts to review safety issues of approved drugs. Some critics argue that such an oversight board should be independent of the FDA, on grounds that the reviewing agency should be separate from the approving agency, and/or that the FDA is captured by industry.(Okie 2005) Counter arguments are greater consistency in decision-making criteria; economies of scale in review if both functions are consolidated in one body; and the potential for any agency to be captured by industry or by consumer groups. Others have called for requiring public disclosure of results from all industry supported clinical trials. Some journals have made public release a condition of publishing results, and some firms have voluntarily committed to release data.(Longman 2005) These policies should increase the information available to physicians and patients. On the other hand, increased risk of post-launch regulatory review, possibly by a body using different risk-benefit criteria than the FDA, may increase post-launch uncertainty for firms.

Some argue for regulatory requirements to perform trials but that all drugs should be available after successful completion of phase II safety trials, leaving patients and physicians to make their own evaluations as to whether expected benefits outweigh risks.(Madden 2004) [8] The counterargument is that by evaluating the evidence on safety and efficacy, including imposing minimum standards with respect to safety and efficacy, the FDA provides a public good. Such information would be underprovided in a free market and costly to assimilate for individual physicians and patients. Although health plans can -- and do -- serve as intermediaries who assess the relative merits of individual drugs, consumers may rightly view

[8] Post launch efficacy trials would be required with results posted on the internet, for consumers to make their own evaluations (Madden, 2004).

health plans as imperfect agents, given their financial stake in controlling drug spending. Moreover, some consumers are uninsured; many others are in health plans with patient populations too small to draw statistically robust conclusions. Strategic competition between firms and logistical problems with data sharing across different IT systems may prevent collaboration.

Moreover, the potential benefits of regulatory standards that establish minimum standards for marketed drugs may have increased with the growth in number of drugs and with insurance coverage. At the time of the 1962 Amendments, there were many fewer drugs on the market and virtually all consumers paid out of pocket. Hence the main potential benefit from a regulatory requirement for efficacy was to protect consumers from wasteful spending on useless drugs; since the drugs available were few and mostly well known, the information burden on physicians or consumers was relatively modest. With the vast expansion in number and complexity of drugs available, with many consumers especially seniors taking multiple prescriptions, the risks of adverse interactions have increased, as have the information burden of remaining informed and the potential costs from being misinformed. Moreover, the growth of insurance coverage has undermined individual consumer's financial incentives to avoid ineffective drugs which could exacerbate the waste from spending on ineffective drugs. Consistent with this, insurers generally do not pay for non-prescription remedies that have not met FDA efficacy standards and hence are barred from making specific health claims.

With regard to safety, tort liability provides an additional (or alternative) incentive for safety. However, if liability rulings or awards are systematically biased, relative to optimal judgments, incentives for safety are biased; moreover, if liability is highly unpredictable, incentives for safety are likely to be excessive. In theory, since the FDA itself employs experts on the design and evaluation of clinical trials and is guided by advisory panels comprised of medical and statistical experts, their decisions should be better informed and more consistent across drugs than decisions of lay juries. A critical regulatory issue for the future is the optimal mix of regulation and tort liability.

IV. Patents

Given the high cost of R&D, patents are essential to induce sustained investment. The pharmaceutical industry benefits from the same patent provisions (20 years from filing) available to firms in any industry, except for the special patent term restoration granted for pharmaceuticals under Hatch Waxman, to restore time lost in clinical trials (see section II). However, pharmaceutical product patents are more readily enforceable and harder to invent around, compared to patents in many other industries. Consequently, many originator pharmaceuticals enjoy an economic life until the patent expires and generic entry occurs. By contrast, the economic life of a medical device is usually much shorter than the patent, because imitative entry occurs long before the patent expires. Because of the necessity and value of patents

for pharmaceuticals, the pharmaceutical industry has been at the forefront of international negotiations over patent provisions for the WTO.

Although a full review of pharmaceutical patents is beyond the scope of this paper, issues that intersect with regulation are briefly reviewed here.

1. Patent Length and Conditions for Generic Entry Material to be added.

2. Patents, "Access", Static Efficiency: Industrialized vs. Developing Countries

Pharmaceutical patents raise the standard issue of static efficiency loss, if prices to consumers exceed marginal cost and result in suboptimal consumption. However, for most industrialized countries that have comprehensive health insurance coverage for drugs with at most modest patient co-payments, this patent-induced tendency for underconsumption is mitigated by an insurance-induced tendency for overconsumption. Probably a greater concern in these contexts is that health insurance reduces the demand elasticity facing the firm and hence creates incentives to charge prices that are significantly higher than would occur due solely to patents. Public insurers' response to this by price regulation is discussed below.

However, the potential for significant static inefficiency and welfare loss due to patent-induced underconsumption remains a serious concern for developing countries, where insurance is limited and most consumers pay out of pocket for drugs. Under the WTO's TRIPS requirements, all WTO members must adopt a patent regime with 20 year product patents (from date of filing) by 2015, with the proviso that governments may grant a compulsory license to generic producers in the event of a "national emergency".[9] The scope of this compulsory licensing provision remains disputed, both with respect to the health conditions and the countries to which it applies, and whether it is *de facto* being undermined by bilateral trade agreements, particularly with the US, that stipulate stricter patent provisions.

In practice, it is an empirical question whether product patents in developing countries necessarily result in a significant welfare loss due to high prices and underconsumption (see for example, Fink, 2001; Watal 2000) . If market demand is in fact highly price-elastic due to low willingness or ability to pay, then profit-maximizing firms would charge prices that are close to marginal cost. In fact, some companies have not bothered to file for patents in several African countries that (in theory at least) would enforce them (Attiran,), suggesting that they perceive little value in patents due to some mix of highly elastic demand, costs of filing and and enforcement costs. If demand is highly elastic such that, even with enforceable

[9] See Article 31
http://www.wto.org/english/tratop_e/trips_e/t_agm3_e.htm

patents, profit-maximizing prices in low income countries would be close to marginal cost, then the welfare loss due to patents is small but so is the incentive to invest in R&D to treat diseases endemic to these countries.

In designing an optimal regulatory frameworks for pharmaceuticals for developing countries, it is important to distinguish between two classes of drugs, global vs. LDC-only drug. For global drugs that treat diseases such as diabetes, cardiovascular conditions or ulcers, that are common in both developed and developing countries, market segmentation and differential pricing can in principle reconcile affordability in LDCs with incentives for R&D: firms can recoup their R&D investments by pricing above marginal cost in high income countries while pricing close to marginal cost in LDCs. In this context, differential pricing (price discrimination across countries) is likely to increase output and hence enhance static efficiency, while also enhancing dynamic efficiency, through quasi-Ramsey pricing for the R&D joint assets.[10] In practice, actual cross national price differences diverge from ideal Ramsey differentials, for many reasons including the risks of external referencing and parallel trade (Danzon and Towse, 2003, 2005), and possibly incentives for regulatory free riding by large purchasers in regulated markets (see below).

Although actual price differentials are not ideal, the theoretical case is strong for establishing regulatory frameworks that limit cross-national price spillovers through external referencing and parallel trade. Under these conditions, patent regimes may function to stimulate R&D for drugs with a significant industrialized market potential, without significant welfare loss in developing countries.[11] Lanjouw (2002) proposes a regime in which firms could opt for patents in either developed or developing countries. The main benefit of such a system, relative to the status quo, would be to reduce uncertainty with respect to patent enforcement and prices in developing countries.

However, for drugs to treat diseases that are endemic only in developing countries, patents are likely to be an ineffective mechanism to achieve the dynamic efficiency goal of stimulating investment in R&D, because consumers cannot pay prices sufficient to recoup R&D investments. In that case the question of static efficiency loss is moot. The very low level of private sector R&D for LDC-only diseases, despite patent regimes in most low income countries, tends to confirm that patents are ineffective in inducing R&D for LDC-only drugs.

In response to the great need but low levels of private sector investments in drugs to treat LDC-only diseases, there has been a recent spate of "push" (subsidy) and "pull" proposals and some initiatives to find new institutional solutions. In particular, a highly diverse set of public private partnerships have developed,

[10] For a discussion of these issues, see for example Dumoulin (2001), Jack and Lanjouw (2003), Malueg and Schwartz (1994), Maskus (2001), Danzon and Towse (2003, 2005), Scherer and Watal (2002).

[11] Institutional arrangements that facilitate differential pricing between the low and high income subgroups in developing countries may also be necessary. Without such segmentation, the optimal single price in a low-income country may be optimized mainly for the small affluent subgroup, and be unaffordable for the lower-income majority.

seeking to combine government and philanthropic funds with private industry expertise and other resources, to address diseases such as malaria, TB, an AIDs vaccine, and many others. The basic issues are outlined in Kremer (2002); for a review of PPP initiatives see Widdus ( ). While these mechanisms to develop new drugs are entirely voluntary, they will depend on regulatory agencies to review the safety and efficacy of any new drugs that result. Developing country governments and international agencies such as the Global Fund, are reluctant to pay for drugs that have not passed regulatory review. Thus as more of these drugs reach clinical trials, the case for developing an regulatory review agency or pathway that is appropriate for these drugs (see section II) will become more pressing.

V. Regulation of Prices, Insurance Reimbursement, Profits etc.

1. The Rationale for Price and Profit Regulation

Regulation of pharmaceutical prices is *a priori* anomalous because the pharmaceutical industry is structurally competitive, with relatively low concentration overall. Although concentration within specific therapeutic categories is greater, the market is contestable, as evidenced by the growing share of new products discovered by relatively new biotechnology firms. Patents grant exclusivity on a specific compound for the term of the patent. But a patent on one compound does not prevent competition from other compounds to treat the same condition. Competitive entry is initiated long before the first compound in a new class reaches the market. Competitor firms can obtain information on each others' drugs in development from patent filings, scientific conferences and other sources that are collated in publicly available databases. Techniques of rational drug design facilitate the development of close substitute compounds in new therapeutic classes. Acemoglu and Linn (2004) show that entry of new drugs responds to expected demographic market size. Specifically, they find that a one percent increase in expected demographic demand results in a four percent increase in entry of NMEs / non-generic drugs and a six percent increase in total number of drugs, including generics. DiMasi and Paquette (2004) find that entry of follow-on compounds has reduced the period of market exclusivity of first entrants to a new therapeutic class from 10.2 years in the 1970s to 1.2 years in the late 1990s. Lichtenberg and Philipson (2002) compare the effect on a drug's net present value at launch of within molecule (generic) competition vs. between molecule (therapeutic) competition. They conclude that the reduction in discounted drug lifetime value from therapeutic competition (most of which occurs while the drug is on-patent) is at least as large as the effect due to post-patent generic entry. Of course, a much higher discount factor is applied to generic erosion because the NPV is measured at launch; still, this study provides an interesting measure of therapeutic competition.

The limited market power that results from patents is reinforced by two other institutional characteristics of pharmaceuticals. First, in industrialized countries obtaining drugs that are authorized to

make health claims requires a prescription from a physician. If physicians are uninformed about drug prices or are imperfect agents for patients, the separation of prescribing from consumption may make demand less elastic.

Second, insurance coverage for pharmaceuticals makes patients less price-sensitive, hence makes the demand facing manufacturers less elastic which would lead them to charge higher prices, in the absence of controls. Co-payments can mitigate the insurance effect, but because co-payments also reduce financial protection, in practice most public insurance plans include only very modest co-payments. To counteract this price-increasing tendency of insurance, both private and public insurers limits the price that they will pay for insured services. In the US, private insurers negotiate drug prices with manufacturers; although large private payers such as Kaiser have significant bargaining power, none have monopsony power and suppliers can and do choose not to supply a particular plan if its offered prices are unacceptably low.

In most industrialized countries with universal national or social insurance plans, the government is either the sole insurer or the regulator of quasi private social insurance funds. Controlling prices as a way to control supplier moral hazard applies to pharmaceuticals as well as to physician fees and hospital charges. For example, Japan has a single fee schedule that sets fees for all medical services, including drugs. Consistent with this view of pharmaceutical price regulation as fundamentally an insurance strategy to control supplier moral hazard, price controls in most countries apply only if drugs are reimbursed by the public health plan. A firm is free to market a drug at unregulated prices once registration requirements are met. It is only if the firm seeks to have its product reimbursed by the public insurance that the price must be approved by the price regulatory body.

2. Pricing and Competition in Unregulated Markets

On-Patent Brands The early literature provides some evidence on competition in pharmaceutical markets before the advent of widespread insurance coverage and associated price controls. Opinion in the economic and policy literature was divided on extent and welfare effects of competition. Some viewed closely substitutable, patented products as wasteful 'me-toos', arguing that patent protection leads to excessive product differentiation and higher prices (for example, Comanor, 1964; Temin, 1980). Under this view, the 1962 Amendments, by requiring proof of efficacy and restricting drug advertising, should have increased price competition. The alternative view is that the availability of substitute products increases price competition, hence can benefit consumers. To assess the impact of the 1962 Amendments on prices, Peltzman (1973) examined average price changes from 1952 to 1962 and a cross sectional analysis for 1958-1961, prior to the 1962 regulations. He found no evidence that the number of NCEs had any net impact on drug price inflation and concluded that, if anything, drug price growth increased after the 1962 Amendments.

Subsequent studies have examined launch prices and price trends over a drug's lifecycle. In a study of launch prices of new drugs introduced between 1958 and 1975, Reekie (1978) found that new drugs that offer significant therapeutic advance were priced above existing drugs but tended to lower price over time, whereas imitators were priced lower initially but tended to increase prices. Similarly, Lu and Comanor (1998) using data for 144 new drugs launched in the US between 1978 and 1987 found evidence of a skimming strategy for innovative drugs and a penetration strategy by imitators. This evidence is consistent with some degree of competition but imperfectly informed buyers, such that sellers offer a low initial price to encourage use and build reputation or loyalty, then raise prices over time (Schmalensee, 1982).

In the US, the nature and extent of competition in pharmaceutical markets has changed with the growth of managed drug coverage in the 1980s and 1990s. Pharmacy benefit managers (PBMs) typically establish formularies of preferred drugs that are selected on the basis of price and effectiveness. Tiered co-payments and other strategies are used to encourage patients and their physicians to the use "preferred" drugs in the class. Such strategies are designed to increase the cross-price elasticity of demand between therapeutic substitutes (and are particularly powerful between generic equivalents, see below). By using formularies to shift market share between therapeutically similar on-patent drugs and hence increase the demand elasticity facing manufacturers, PBMs are able to negotiate discounts in return for preferred formulary status. These discounts are confidential, hence detailed analysis is not available. However, the limited evidence available does confirm the theoretical prediction that discounts are larger to purchasers that have tight control over drug use, such as Kaiser, and in classes with several close substitute products (CBO, 1994; Danzon and Furukawa, 2003) Evidence that new drugs are launched at list prices below the price of established drugs in the same product class and that the discount is greater, the greater the number of existing drugs in the product class (Boston Consulting Group, 1993) indicates that competition does reduce prices even in for unmanaged consumers.

Although discounting through confidential, electronic rebates to PBMs, as agents of payers and consumers, has no doubt stimulated price competition, it has been attacked on several grounds. First, because it is essentially a system of price discrimination, those who pay higher prices feel aggrieved and indeed the results would strike many as inequitable. Specifically, the largest discounts go to plans with tightly controlled formularies that tend to attract relatively healthy, privately insured non-seniors, whereas uninsured and other cash-paying customers, including many seniors, face the highest prices. This differential in manufacturer prices is amplified for retail prices because PBMs also negotiate discounts in pharmacy dispensing margins, relative to unmanaged dispensing fees pharmacies charge to cash-paying customers. Combining the manufacturer and pharmacy discounts, consumers with managed drug benefits

face at least 25% lower drug costs (GA0,) compared to uninsured patients, many of whom are seniors.[12]

Second, discounting has been challenged by retail pharmacists in antitrust litigation alleging collusive pricing and price discrimination by drug manufacturers (Scherer, 1996; Danzon, 1996). Dispensing pharmacies do not receive the same discounts given to PBMs because pharmacies cannot - and arguably should not attempt to – independently influence a physician/patient's choice between therapeutic substitutes. This litigation conspicuously excluded off-patent, multisource drugs, because for these drugs the discounts go to the pharmacies, because they are the decision-makers in choosing between generically equivalent versions of a prescribed compound(see below). Under the settlement of this litigation, manufacturer discounts are to be made available on the same terms to all purchasers; however, because PBMs design the formularies that drive therapeutic substitution, they remain the main recipients of discounts on on-patent drugs, although wholesalers do receive modest prompt payment and volume-related discounts.

Third, incentives for discounts to private payers have been reduced by the matching requirement, that manufacturers of brand drugs give to Medicaid the "best price" given to private payers or a 15.1% discount off Average Manufacturer Price, whichever is lower. This best price provision effectively imposes a significant tax on discounts to private payers, because Medicaid on average accounts for 12-15 percent of drug sales and Medicaid demand is totally inelastic with respect to this discount. Theory suggests that this best price provision would reduce best price discounts to private payers and this is confirmed by evidence from several studies (CBO 1993; CBO 2005b).

Finally, because the discounts are confidential, payers who contract with PBMs as agents accuse the PBMs of pocketing rather than passing on the discounts. Since the Medicare drug benefit will be delivered by competing, private "prescription drug plans" similar to PBMs, both Medicare (that will heavily subsidize the benefit) and seniors (who contribute to premiums, pay significant co-payments and must choose between competing plans) have demanded "price transparency". However, CBO estimated a significantly higher cost for a variant of the Medicare drug benefit that required price transparency, under the assumption that transparency would erode drug manufacturers' competitive incentives to discount and hence would lead to higher drug prices. The final MMA legislation requires PDPs to reveal discounts in aggregate but not drug-specific prices.

Generics In most US health plans, reimbursement for multisource drugs (off-patent drugs with at least one generic, in addition to the originator) is designed to create strong incentives for decision-

[12] The 2006 Medicare drug benefit should enable insured seniors to get discounts at least as large as privately insured patients; however, other uninsured patients will continue to face higher prices.

makers to prefer generics over their brand equivalents. These regulatory and reimbursement structures in turn generate intense generic price competition and large generic market shares. Specifically, most HMOs, PBMs and Medicaid plans cap pharmacy reimbursement for multisource drugs at the price of a low priced generic, the MAC or maximum allowable charge for that compound. If the patient wants the originator brand, he or she must pay the difference between the brand price and the MAC (or a third-tier co-pay, in some tiered formularies). Since the 1980s, most states have overturned traditional anti-substitution laws and now authorize pharmacists to dispense any bioequivalent generic, unless the physician explicitly requires the brand.

Since pharmacists capture any margin between the MAC and their acquisition cost, pharmacists have strong incentives to seek out cheap generics. For generic drug manufacturers, the primary customers are large pharmacy chains and group purchasers for independent pharmacies. This highly concentrated and price-sensitive pharmacy demand creates incentives for generics to compete on price. If the 1984 Hatch Waxman Act opened the door to cheap and prompt generic entry in the US, generic substitution programs adopted by PBMs, HMOs and Medicaid in the late 1980s and 1990s stimulated generic market shares while MAC reimbursement drives generic price competition. Masson and Steiner (1985) show that for a sample of 37 multisource drugs in 1980, pharmacists obtained the generic at an average price 45 percent lower than the brand, but the difference at retail was only 24.3 percent, because the pharmacist retained a higher average absolute margin on the generics. Similarly, Grabowski and Vernon (1996) show that for 15 drugs whose patents expired between 1984 and 1987, the average absolute margin was roughly 40 percent higher on the generic. More recent anecdotal reports confirm these findings.

Most studies of generic drug markets focus on the effects of the 1984 Hatch Waxman Act on generic entry and on the effect of generics on prices, promotional activity and market shares of brand drugs. Since market conditions have evolved in the 1990s with the growth of managed drug benefits, the findings of these studies are significantly time and context-dependent. Grabowski and Vernon (1992), using data on patent expirations that spanned the 1984 Act, find that generic prices were significantly inversely related to number of generic competitors, but some brand prices increased after generic entry. Frank and Salkever (1992) show that a brand manufacturer may rationally increase the brand price following generic entry, as a response to market segmentation in which generics attract the price elastic consumers, leaving the brand with the price-inelastic, brand-loyal consumers. Brand advertising may decrease, since much of the benefit accrues to generics due to substitution; conversely, generics have no incentive to advertise if they are viewed as substitutable.

Caves, Whinston and Hurwitz (1991) analyze post-patent pricing and promotion for 30 drugs whose patents expired between 1976 and 1987. They find significant reduction in brand promotion even before patent expiration. The net effect of less promotion and lower generic prices is that quantity sold does

not increase significantly after patent expiration. All of these studies underestimate generic penetration since the growth of managed drug benefits in the 1990s. Whereas Caves, Whinston and Hurwitz (1991) find that pharmacists were quite conservative in exercising their right to substitute a generic, for recent patent expirations, the originator loses up to 80 percent of the market within several months of patent expiry in the US.

Summarizing, conclusions on competition in the brand and generic pharmaceutical industries depend on the context, in particular, on the regulatory structure, insurance arrangements and resulting incentives for physicians, pharmacies and patients, which interact to determine manufacturer demand elasticities and hence optimal manufacturer pricing strategies. Similarly, estimates of demand elasticities depend on the context, depending on such factors as whether the drug is on-patent or generic, on whether the price is the co-payment to the patient or the full drug price to the payer, and on relevant pharmacy and physician incentives. Several studies of demand elasticity are reviewed in Anessi (1997).

3. Forms of price and reimbursement regulation

Design of the optimal structure of price regulation or other controls on pharmaceutical spending is a complex problem that has not been adequately addressed in the literature. The one clear conclusion is that no country has a good solution. As noted earlier, market power of pharmaceuticals derives from patents and from comprehensive insurance coverage, hence standard regulatory models of price regulation are not appropriate. Standard models of optimal insurance contracts are also inadequate. These tend to focus on the design of consumer co-payments to constrain moral hazard (for example, Pauly, 1968; Zeckhauser, 1971; Ma). Since higher co-payments reduce financial protection, optimal co-payments for drugs may be too low to provide much incentive, especially for chronic and expensive drugs and the concentration of spending by patients with multiple prescriptions. Optimal provider cost-sharing has been analyzed for physician and hospital services (for example, Ellis and McGuire, 1991) but not for pharmaceuticals. Moreover, the optimal insurance/reimbursement contract for drugs must deter not only insurance-induced overuse by patients/physicians but also excessive prices by manufacturers, while paying prices sufficient to reward appropriate R&D.

In practice, the structure of pharmaceutical price and reimbursement regulation differs across countries and continually evolves. This review focuses on the main prototypes and evidence of their effects.

Direct Price Limits

Under direct price regulation, as used in France, Italy, Spain, Japan etc. the initial launch price and any price increases must be approved as a condition of reimbursement, and price decreases may be mandated. Most countries use one or both of two criteria in setting prices: (1) comparison with other, established drugs in the same class, possibly with mark-ups for improved efficacy, better side effect profile

or convenience, and for local production (hereafter "internal benchmarking"); and (2) comparison with the price of the identical product in other countries (hereafter "external benchmarking").[13]

Internal benchmarking. Effects of regulation through internal benchmarking differ depending on the details of each country's system, including mark-ups for innovation and other factors. Hypothesized effects include: adjustments to the price profile (Anis and Wen, 1998); distortions of R&D focus; distortions in number and location of manufacturing plants; and effects on R&D location.

If post-launch price increases are not permitted, a drug's real price declines over its life-cycle. Consequently, if follow-on products are benchmarked to an old drug, the real launch price declines for successive entrants in a class. In Japan, because physicians traditionally dispense drugs and capture any margin between drug's reimbursement and its acquisition cost, manufacturers tend to discount below the reimbursement price in order to increase physician margins and hence gain market share. The government audits acquisition prices bi-annually and revises down the reimbursement price to leave only a 1% margin, until the next rounds of competitive price cuts. This system of declining post-launch prices allegedly traditionally created incentives for Japanese pharmaceutical firms to focus their R&D on frequent, minor improvements of existing products in order to obtain higher prices, rather than invest in the major innovations necessary to achieve global competitiveness.[14]

Such price regulatory systems are also widely alleged to be used for industrial policy goals, granting higher prices for products that are locally produced, despite the 1989 EU Transparency Directive which requires that regulations be 'transparent' and neutral with respect to country of origin. Such biased regulation creates incentives for nonoptimal location and/or an excessive number of manufacturing plants, if these excessive production costs are "offset" by higher prices (Danzon and Percy, 1996).

Although secondary (processing and packaging) manufacturing facilities may plausibly be located disproportionately in countries that reward domestic manufacturing through their pricing systems, the opposite charge is made with respect to R&D. Specifically, the pharmaceutical industry sometimes argues that low regulated prices discourages investment in R&D in those countries. Both the incentive effect of lower expected profits and the financing effect of lower retained earnings could reduce R&D. It is empirically true that most R&D is located in countries with relatively free pricing, such as the US and the UK. However, the causal relationship is unclear. In theory, given the potentially global market for innovative drugs, and extensive in- and out-licensing networks that enable small firms to reach global

[13] Although some countries, including Italy, have attempted to base prices on costs, this approach is not widely used because of the difficulty of obtaining accurate measurement of costs. Measuring R&D cost is particularly problematic, because it occurs over many years, includes the cost of failures and foregone interest, and is largely a joint cost that must be allocated across global markets.

[14] Thomas (1996) discusses other factors, including relatively weak efficacy requirements for drug approval, that may have contributed to the relatively weak international competitiveness of Japan's pharmaceutical industry, compared to its prowess in other high technology industries.

markets regardless of their location, there is no necessary connection between domestic price regulation and firms' location of R&D. Access to world class scientific research and a large pool of human capital surely also play a (larger?) role. As governments in many countries are establishing tax-subsidized science parks to try to attract pharmaceutical and biotechnology R&D, more may be learned about the relative importance of various factors in R&D location.

External benchmarking Whereas internal benchmarking compares the price of the new drug to the prices of competitor products, external benchmarking uses as the comparator the mean, median or minimum price of the same drug in a designated set of countries. For example, Italy uses an average European price, Canada uses the median price in five European prices plus the US and Japan, etc. External benchmarking thus limits the manufacturer's ability to price discriminate across countries. Predicted effects include convergence in the manufacturer's target launch prices across linked markets, with launch delays and non-launch becoming an optimal strategy in low-price countries, particularly those with small markets. Parallel trade, which is legal in the EU, has similar effects to external referencing, except that it generally only affects a fraction of a product's sales. Several studies provide evidence consistent with these predictions: Danzon, Wang and Wang, 2004; Kyle, 2004; Lanjouw, 2004; Danzon and Epstein, 2005 forthcoming.

Welfare effects of regulatory pressures for price convergence across countries are theoretically ambiguous but likely to be negative. Analyses of price discrimination vs. uniform pricing show that price discrimination increases static efficiency if output increases. That differential pricing increases drug use seems plausible, given the evidence of delays and non-launch of new drugs in low price countries. Moreover, Ramsey pricing principles suggest that differential pricing also contributes to dynamic efficiency (Ramsey, 1927; Baumol and Bradford, 1970).[15] So far, external referencing and parallel trade apply mostly between countries at fairly similar levels of income, notably within Europe. Welfare losses would likely be much larger if referencing or importation were authorized directly between high and low income countries, or indirectly via middle income countries. The proposed US Health Security Act of 1994 would have limited drug prices in the US to the lowest prices in a group of 22 other countries, including several with much lower incomes than the US. More recently, the US is seriously considering proposals to legalize drug importation from a broad group of other countries. Aside from the safety issues raised by drug importation, linking the dominant US market to other smaller, lower income markets could have serious negative effects on price and availability of drugs in those countries. From a global welfare perspective, forms of price regulation that are country specific are likely to yield lower welfare loss than regulatory systems that attempt to control one country's prices by referencing prices or importing drugs from other countries.

[15] For analysis of differential pricing in the context of developing countries, see Danzon and Towse, 2003, 2005 forthcoming; Jack and Lanjouw ( ).

Reference Price Reimbursement Limits

Some countries, including Germany, the Netherlands and New Zealand, have established reference price reimbursement systems that limit the reimbursement for drugs in designated groups. Under RP, products are clustered for reimbursement based on either the same compound (generic referencing) or different compounds with similar mode of action, for the same indication etc (therapeutic referencing). All products in a group are reimbursed the same price per daily dose – the reference price (RP). The RP is usually set at the price of say the cheapest (or the median, the thirtieth percentile etc.) of drugs in the group. Manufacturers are permitted to charge prices above the RP, but patients must pay any excess. In practice, many manufacturers drop their prices to the reference price, suggesting that demand is highly elastic when patients must pay.

Reference price reimbursement resembles price regulation with internal benchmarking to similar products, but with critical differences that make RP potentially more constraining. First, whereas informal benchmarking may permit higher reimbursement for drugs with superior efficacy or fewer side-effects, under RP the reimbursement is the same per daily dose, for all products in a group, and obtaining higher reimbursement for a more effective drug requires establishing a separate class within the same therapeutic category. The RP classification system is therefore critical, and assignment of individual drugs is often litigated. Second, therapeutic RP systems typically cluster compounds without regard to patent status. Consequently, if the RP is based on the cheapest product in the cluster, once one patent expires and generic entry occurs, reimbursement for all products in the group drops to the generic price, thereby effectively truncating patent life for the newer products in the group, unless patients are willing to pay surcharges. The magnitude of this patent-truncating effect is greater, the broader the definition of reimbursement clusters and the more price-competitive the generic market. Therapeutic RP is predicted to reduce incentives for R&D in general, if the patent-truncating effect is large. Negative effects on R&D incentives are likely to be greatest for follow-on products or line extensions of existing drugs. Whether any such reduction would be a welfare-enhancing, by eliminating wasteful R&D, or a welfare-reducing, by eliminating potentially cost-effective new drugs and reducing competition in a class, is obviously context-specific and cannot be predicted a priori. More generally, because incentives for R&D depend on global expected revenues, the effects of RP so far are not expected to be large because so far no major market has long experience with therapeutic RP. Thus the experience to date is insufficient to predict the likely effects on R&D if the US, with its large share of global revenues and highly price-competitive generic market, were to adopt therapeutic RP.

Although Germany adopted RP for some classes starting in 1989, new patented drugs were exempt from 1996 to 2004. Moreover, in interpreting the German experience with RP and extrapolating to other countries such as the US, it is important to note that the generic market is more price-competitive in the US

than in Germany, where most generics are branded and pharmacies had limited authority and weak financial incentives to substitute cheaper generics.[16] Moreover, Germany -- like all other countries with RP or price regulation – adopted multiple price and spending controls simultaneously. Identifying the separate effects of RP and other constraints is therefore problematic.

The early literature on RP is summarized in Lopez-Casasnovas and Puig-Junoy (2000, 2001). Early evidence from Germany confirmed that brand drugs generally dropped their prices when RP was introduced, as theory predicts (Maasen, 1995). However, both theory and evidence suggest that dynamic price competition over time is weak under RP, because firms have no incentive to reduce prices below the RP. Zweifel and Crivelli (1996) analyze firms' response to RP using a duopoly model; where RP applies to classes with multiple firms, oligopoly or monopolistic competition models may be relevant. Danzon and Ketchum (2003) provide empirical evidence on effects of RP in Germany, the Netherlands and New Zealand, the three most comprehensive RP systems. This evidence suggests that RP had little effect on average drug prices or drug availability in Germany or the Netherlands, but that effects on prices and availability were significant in New Zealand, which used broader classes and where the regulatory agency explicitly required RP-reducing price cuts as a condition of admitting new drugs to reimbursement.

In theory, since RP limits only the insurer's reimbursement, patients may be willing to pay a surcharge if a drug truly offers greater therapeutic benefits. But patients may be imperfectly informed about the risks and benefits of individual drugs, and physicians may be reluctant to spend the time required to provide information , since such time is unreimbursed and may have a significant opportunity cost. Some manufacturers may choose to charge prices above the RP, despite high demand elasticities, to avoid price spillovers to other markets. For example, when British Columbia adopted RP, some manufacturers retained prices above the RP, plausibly to avoid undermining potentially higher prices in other Canadian provinces. If manufacturers do charge surcharges, patients may face significant co-payments, with possible effects on drug choice and health outcomes. The evidence on patient health outcomes under RP is mixed: some studies find no evidence of adverse effects, while others find an increase in adverse outcomes, possibly because patients switched to less appropriate drugs to avoid surcharges. The risks of such adverse effects depend on the degree of substitutability between drugs, which varies across therapeutic classes. For this reason, Australia and British Columbia only apply RP to a select set of therapeutic classes in which drugs are considered highly substitutable for most patients.

Drug Budgets and Expenditure Controls

[16] In Germany, pharmacies must dispense the brand prescribed by the physician and may substitute a generic only if the script is written by generic name. Until 2004, German pharmacies were paid a percentage of the price of the drug they dispensed, hence had no financial incentive to seek out cheaper generics. Not surprisingly, in this system generics compete on brand rather than price.

Price or reimbursement controls alone do not control the growth of drug spending, which is also driven by prescription volume and "mix", that is, switching from older, cheaper drugs to newer, higher priced drugs. Most countries that initially controlled just price or reimbursement have added other measures to limit total drug spending. Specifically, from 1993 - 2003, Germany had a drug budget (limit on aggregate spending), with physicians and the pharmaceutical industry nominally at risk for successive tiers of any overrun. Physicians responded initially by reducing the number of prescriptions and switching to cheaper drugs, leading to a 16 percent reduction in drug spending in the first year of the budget (Munnich and Sullivan, 1994). Schulenburg et al.(1994) report that referrals to specialists and hospitals increased, because the drug budget excluded inpatient drugs. Thus the overall budget saving was less than the saving in outpatient drug costs. Germany's aggregate drug budget was abolished in 2003, because enforcing the repayment of overruns was practically and politically problematic. Some regions have attempted physician-specific budgets. One reason this approach has not been widely adopted is that payers lack the information needed to achieve appropriate risk-adjustment of each physician's patient population. France has a limit on total drug spending that is enforced by limits on each company's revenues. Overruns are recouped by price cuts and mandatory rebates targeted at offending therapeutic classes and companies. Similarly, since 2001 Italy limits drug spending to 13 percent of health spending; overruns have been recouped by price cuts in major therapeutic classes.

Since expenditure caps that are enforced by price cuts imply a price-volume trade-off for manufacturers, one potential – and intended – effect is to reduce manufacturers' incentives to grow volume through promotion. However, penalties that apply collectively by all firms have only weak effects on firm-specific incentives in the absence of collusion. Company-specific revenue limits, as in France, create more powerful incentives to constrain promotion but also undermine incentives for R&D. As with price and reimbursement controls, these R&D incentive effects are negligible for controls that apply in small markets. Such effects would be more significant if drug spending caps enforced by price-volume offsets were adopted in the US or EU-wide.

Profit or Rate-of-Return Controls

The UK is unique among industrialized countries in regulating the rate of return on capital, leaving manufacturers (relatively) free to set the price of individual drugs. The UK Prescription Price Regulation Scheme (PPRS) is renegotiated every five years between the patented pharmaceutical industry and the government. The PPRS limits each company's revenues from sales to the UK National Health Service as a percent of their capital invested in the UK, with specified limits on deductible expenses to pre-empt incentives for expense padding. The allowed rate of return is around 17-21 percent; excesses can be repaid directly or through lower prices the following year. Companies with minimal capital in the UK can

substitute a return-on-sales formula.

Simple theory predicts that pure rate of return regulation induces excessive capital investments and lower productivity (Averch and Johnson, 1962). For multinational companies, the costs of distortions may be small if capital can be allocated across countries at relatively low cost in order to maximize revenues. Such flexibility becomes more constrained as more regulatory systems link their prices or reimbursement to local investment. In a study of the effects of such biased regulatory schemes in the UK, France and Italy on labor and total factor productivity, Danzon and Percy (1996) found that although the rate of growth of capital and labor in the UK pharmaceutical industry has been high, relative to other UK industry and relative to pharmaceuticals in other countries, it has not been biased towards capital relative to labor, possibly because the permitted company-specific rate of return may depend on its employment growth. Overall, the UK experienced relatively high total factor productivity growth, compared to other regulated and unregulated countries.

With respect to effects on drug prices, the UK is generally considered to have higher brand prices than those in the regulated markets of France, Italy and Spain. Consistent with this, the UK has a relatively large parallel import share, whereas the price regulated markets of France, Italy and Spain are parallel exporters. Precise price differentials are sensitive to the sample of drugs, the time period and the exchange rate (see, for example, Danzon and Kim, 1998; Danzon and Furukawa, 2003). The UK's overall spending on drugs, either as a share of health spending or per capita, is not out of line with other EU countries, plausibly reflecting other factors, including a relatively high generic share, and a structure of physician reimbursement that creates incentives for cost-conscious prescribing without cream-skimming.[17]

Cost-Effectiveness Requirements

Australia, Canada, New Zealand and the UK require a formal review of the cost-effectiveness of a new drug as a condition of reimbursement by national health systems; in other countries, such data are used less formally to support price negotiations. For example, in 1999 the UK established the National Institute for Clinical Excellence (NICE) to review evidence on the costs and outcomes of technologies expected to have major health or budgetary impact, including drugs, relative to current treatment, using standard metrics of the cost per quality adjusted life year (QALY). Costs reflect not only the price of the drug but also associated medical costs, such as reduced inpatient days or doctor visits. A similar expert body to review effectiveness was established in Germany in 2004, and others are under debate in some other EU countries and in the US. Adding costs and hence cost-effectiveness to the purview of these bodies seems a likely next

[17]Primary care physicians are organized into primary care groups, by locality. Each group must serve all residents in its area and receives a global budget for their costs. Thus spending more on drugs means less money for other services.

step.

4. Effects of Regulation on Prices

Cross-national comparisons of drug prices vary significantly, depending on the time period, sample of drugs used, the price index methodology used, including unit for measuring price (grams, units, daily doses), consumption weights and exchange rates. Most price comparisons have been biased by use of very small, non-random samples including only branded drugs, and have not adhered to standard index number methods (for example, GAO, 1992, 1994). The exclusive focus on branded drugs tends to bias comparisons in favor of countries with strict price regulation. Regulation and competition are to some degree substitutes: less regulated markets tend to have higher brand prices but larger generic market shares and lower priced generics (Danzon and Chao, 2002; Danzon and Furukawa, 2003).

5. Price Regulation: Lessons Learned and Future research

The research of the 1960s, 1970s and early 1980s focused on effects of regulation of market access, focusing more on measuring the costs of market delay with less success in measuring any benefits from reduced risks or more appropriate drug use. In the 1990s attention focused more on design of price regulatory systems, first to control prices and subsequently to control total drug spending, while preserving access for patients and incentives for R&D. Although much useful research has been done, there remain many unanswered questions on the optimal design of insurance and price regulatory systems to achieve appropriate use of existing drugs and prices that strike a reasonable balance between short run spending control and incentives for R&D for the future.

Useful lessons have been learned on the specific effects of different regulatory strategies but many unanswered questions remain. The evidence from Germany shows that placing physicians at financial risk is a potent weapon to limit drug spending. But a collective budget is likely to be a blunt weapon in the long run. Physician-specific budgets provide stronger incentives but this may lead to undesirable cream-skimming if budget parameters cannot be appropriately risk-adjusted to reflect differences in patient characteristics (see Newhouse).“Silo budgeting” that places separate spending limits on different medical services – drugs, hospitals, physicians – create perverse incentive for cost shifting between the budgets, whereas cost-effective substitution between medical services is essential to achieve the maximum value from total health expenditures. Designing appropriate physician risk-sharing for drugs is an important issue for future research.

In theory, reimbursement decisions based on cost-effectiveness offer a more informed and more efficient mechanism than less analytic internal benchmarking or reference price reimbursement. Under CE, more effective/safer drugs can charger higher prices and still be cost-effective relative to less effective/ safe

drugs. Moreover, if costs and effects are measured using appropriate guidelines, decisions can in theory reflect all relevant social costs and benefits and be more consistent across drugs than is likely with more ad hoc price regulatory schemes. More appropriate regulatory mechanisms for reviewing prices implies better incentives for both R&D and prescribing.

Although CE offers a more appropriate criterion for drug price review than other widely used criteria, important details remain unresolved. One concern is that the data available for evaluating cost-effectiveness at launch are based on controlled, pre-launch clinical trials, which may not accurately reflect the costs or effects of a drug in actual usage. Updating the CE analysis with post-launch data from actual use is possible in principle, however, it is costly, is potentially less accurate due to non-random treatment assignments, and canceling reimbursement post-launch may be politically difficult. Nevertheless, integrating pre- and post-launch data is likely to become the norm as databases and statistical techniques improve. A second limitation of cost-effectiveness analysis is that it yields a ceiling or maximum price at which a drug is cost-effective, for a payer-specific CE threshold; however, CE alone does not yield the most appropriate price, because the drug would be even more cost-effective at a lower price. Thus although review of cost-effectiveness is becoming a necessary condition for reimbursement in an increasing number of countries -- and the US Medicare drug benefit may follow -- CE evaluation has supplemented but not replaced other price and expenditure regulatory systems in countries that seek to control drug spending.

6. Profitability and Rates of Return

The pharmaceutical industry is widely perceived to earn excessive return. Accurate measurement of profits is particularly problematic for pharmaceuticals because capital investments are primarily in intangible R&D and promotional capital, while sales occur globally and over a product life of 20 years or more. Several approaches have been used to measure profitability. One approach attempts to adjust accounting rates of return to better account for investments in intangible capital of R&D and promotion. Standard accounting practices treat R&D and promotion spending as current expenses rather than as investments in intangible capital. This leads to upward bias in accounting rates of return for industries with relatively high intangible investments. Clarkson (1996) illustrates the effects of these adjustments for firms in fourteen industries for the period 1980-1993. Before adjustment, the average accounting rate of return on equity for the fourteen industries is 12.3 percent; the pharmaceutical industry has the highest return of 24.4 percent. After adjustment for intangible capital, the average is 10.2 percent compared to 13.3 percent for pharmaceuticals, which is less than the adjusted return for petroleum, computer software and foods.
A second approach uses the Lerner index of price relative to marginal production cost. Caves, Whinston and Hurwitz (1991) estimate the ratio of the price of originator drugs relative to generic price several years after patent (a proxy for marginal cost) at roughly 5. However, this price ratio at patent expiry overstates the

average Lerner index over the life-cycle, because prices of originator drugs tend to rise and marginal costs decline with drug time since launch. More fundamentally, a Lerner index based on short-run marginal production cost in one country cannot provide an accurate measure of profitably for global products with high R&D investments, such as pharmaceuticals.

A third – and conceptually more correct approach -- measures the rate of return on investment in a cohort of drugs, using discounted cash flow estimates of costs and returns. Grabowski and Vernon (1990, 1996, 2002) estimate the return on R&D for new drugs introduced in the 1970s, early 1980s and 1990s, respectively. Market sales data for the US are used to estimate a 20-year sales profile; global sales are estimated using a foreign sales multiplier. Applying a contribution margin to net out other, non-R&D costs yields a life-cycle profile for net revenue, which is discounted to present value at launch using the estimated real cost of capital (10 – 11 percent). This NPV of net revenues is compared to estimates of the average capitalized cost of R&D per NCE, at launch. Grabowski and Vernon conclude that the 1970s drug cohort on average earned a return roughly equal to their cost of capital; the 1980s cohort on average yielded a positive net present value of $22.2m, or an internal rate of return of 11.1 percent, compared to the 10.5 percent cost of capital. Similarly, results for the 1990s cohort show a small, positive excess return. Given the large number of assumption, confidence intervals are not reported. In all three time periods, the returns distribution is highly skewed, such that only the top 30 percent of drugs cover the average R&D cost. This conclusion would be modified but probably remain generally true, if the distribution of revenues were compared to a reasonable distribution of R&D costs across therapeutic classes, rather than the average R&D cost. Grabowski and Vernon (1996) use simulation analysis to show that an important implication of this skewed distribution of returns is that regulatory strategies that target these'blockbuster' drugs while on patent could significantly reduce expected average returns and hence reduce incentives for R&D. By contrast, a competitive strategy that permits high prices for patented drugs but then promotes generic competition after patent expiry has a much less negative effect on incentives for R&D, because loss in sales revenue that occurs late in the product life is more heavily discounted.

Although this cohort rate-of-return approach in theory provides the most accurate measure of returns to R&D, it is arguably of limited relevance for policy in an industry with low barriers but long lead times for entry and high unpredictability of science and market risk. Specifically, if analysts estimate returns that either exceed or fall short of competitive levels, this plausibly reflects either measurement error of the analysis or market disequilibrium that is probably already being corrected by competitive entry, such that the analyst's estimate is obsolete before it is made. In the absence of significant barriers to entry to research activities for new or existing firms, if pharmaceutical R&D were to generate above normal expected returns, competitive entry would occur until expected returns just cover the cost of capital. Such competitive adjustments are not smooth or instantaneous, due to risks and time lags in R&D, and

continually changing market and regulatory conditions. Thus the actual realization of returns may differ radically from that anticipated when the R&D was initiated.

For pharmaceuticals, the evidence indicates extensive competitive entry to exploit R&D opportunities, hence a reasonable assumption is that entry occurs until expected profitability falls to normal levels. The more important policy question is whether the resulting rate of R&D yields a flow and mix of new drugs that is socially optimal. In this model, changes in the regulatory and reimbursement environment may affect profitability in the short run. But in the long run, the rate and mix of R&D readjusts such that normal returns are realized on average. Whether the resulting R&D expenditures entail significant duplicative investment is an important issue. Henderson and Cockburn (1996) provide some evidence against this idea, but not a definitive rejection. The current trend of payers to demand evidence of cost-effectiveness relative to existing drugs as a condition for reimbursement, reinforces incentives for manufacturers to target R&D towards innovative therapies and away from imitative drugs. The great *ex ante* uncertainty as to the ultimate therapeutic value and timing of new drugs implies that *ex post* realizations will still yield some "me-too" drugs. Even the optimal number of me-toos is uncertain, given their value as a competitive constraint and in improving therapies for some subsets of patients.

7. Industry Structure and Productivity: Regulation or Technology?

Several studies have examined the effects of regulation and other factors on industry structure and economies of scale in R&D. Temin (1980) analyzed the impact of regulatory and technological change on the structure of the US pharmaceutical industry from 1948 to 1973. He concludes that the size of drug firms increased dramatically during this period with much of the growth concentrated in large firms. Grabowski and Vernon (1976, 1977) suggested that regulation-induced increases in cost and risks of R&D created scale economies that resulted in the concentration of innovation in large firms. Thomas (1990) shows that the decline in NCE introductions around 1962 was concentrated in the smallest firms, many of which ceased R&D. Thomas (1996) extends the argument that strict safety and efficacy regulation in the US and UK led to a shakeout of smaller, less innovative firms and concentration of innovative effort in larger firms.

More recently, the structure of the pharmaceutical industry has undergone fundamental change. The biotechnology and genomics revolutions of the 1980s and 1990s have reduced or eliminated the advantages of size, at least for drug discovery. Previously, the chemistry basis of drug discovery implied an advantage for large firms that had large libraries of compounds, often created by their in-house chemists. Now, the basis for drug discovery has shifted to micro-biology and associated sciences, shifting comparative advantage to smaller firms, often spun out from academic research centers. Large firms have continued to grow larger, mostly through merging with other large firms, by aquiring biotechnology companies or inlicensing their compounds. Although the large horizontal mergers have often been rationalized on

grounds of economies of scale and scope in R&D, in fact R&D productivity of large firms has declined. A growing number of new drug approvals are biologics, originated by smaller firms. Initially, smaller firms tend to specialize in discovery research, forming alliances of various types with larger firms for late-stage clinical trials and marketing, where experience and size play a greater role. Conversely, large firms rely increasingly on in-licensing – both tools and target compounds - from smaller firms. Thus the evidence from the post-1962 era, when increased regulatory costs reportedly contributed to increased industry concentration and disadvantaged small firms, has not been repeated in response to regulatory cost increases of the 1990s.

VI. Promotion

1. Trends in Promotion

Promotion by manufacturers is an important mechanism whereby physicians, consumers and payers learn about drugs. In 2003 the industry spent $25.3 billion on promotion or 17.1% of sales– similar to several other industries in which product differentiation via advertising is an important factor in influencing demand such as toys and cosmetics (Frank, RG 2002; Berndt, 2005).[18], [19] This estimate of total promotion spending does not include the promotion-related components of pre- and post-launch clinical trials. Of the reported total, almost two-thirds ($16.3 billion) reflects free samples distributed to physicians (Berndt 2005) for patient use. These samples are valued at average wholesale price (AWP) which is a manufacturer list price that significantly exceeds the economic cost.[20] The next largest components of promotional spending were physician detailing ($4.5 billion), DTC ($3.7 billion), hospital detailing ($819 million) and medical journal advertising ($448 million) in 2003(Berndt 2005).

Promotional spending overall has grown substantially over the last decade, and the ratio of promotional spending to sales has increased somewhat, from 14.1% in 1996 to 17.1% in 2003. DTC spending has grown most rapidly over the last 10 years, from just $12 million in 1989 and $791M. in 1996 –prior to the 1997 FDA reinterpretation of the DTC guidelines -- to $3.2 billion in 2003 (Palumbo FB 2002; Berndt 2005). However, pharmaceutical promotion spending for the period January - June 2005 was only 0.4 percent higher than the same period in 2004, compared to an overall 5.7 percent increase in all

[18] The industry-wide promotion-to-sales ratio is also a biased measure for the branded drug industry overall, to the extent that the sales figure in the denominator includes OTC and generic sales for the included firms, but omits brand firm sales of some other firms.
[19] In 2003, the reported promotion spending is less than the spending on R&D of $34.5 billion in 2003 (Berndt 2005), but the R&D spending measure includes R&D spending in the US for some firms domiciled outside the US. More generally, any country-specific measure of R&D-to-sales is somewhat arbitrary for multinational firms with global sales but R&D located in at most a few countries.
[20] A more accurate measure of the true cost of samples to firms lies somewhere between the marginal production cost and the actual price the manufacturer might have received, had the patient filled the prescription and paid for the drug.

advertising spending during the same period (Henderson, 2005). The industry trade association PhRMA has issued voluntary guidelines for DTC and some firms have voluntarily committed to limiting their DTC, at least in the first months post-launch. Although DTC was growing before the 1997 FDA Guidance, that Guidance clearly did increase the share of broadcast ads, from under 30 percent prior to 1997 to almost two-thirds in 2002 (Rosenthal, 2002). DTC spending is concentrated in particular therapeutic categories, with significant variation across drugs in a class. An examination of 1999 data indicates that of 391 major branded drugs, just 18% spent any on DTC (Neslin, 2001, cited in Berndt 2005). Moreover, in the first six months of 2004 DTC spending for the top 20 drugs accounted for 65.1% of all DTC spending. The top five therapeutic categories for DTC spending as of 2000 were antidepressants, antihistamines, antihyperlipidemics, nasal sprays and proton pump inhibitors (Rosenthal MB 2002; Berndt 2005). Currently New Zealand is the only other country to allow DTC. Some other countries prohibit samples, and indeed there may be little value in free samples in countries where patient co-payments are low. Other countries apply at least indirect limits on promotional spending, such as the UK limit on promotion that is deductible for calculating the return on capital.

2. Regulation of Promotion: Background and Issues

As discussed in Section II, regulation of prescription drug promotion in the US has been under the control of the FDA since the 1962 Amendments. This statute restricted promotional claims to facts established in clinical trials, which excluded promotion of unapproved uses. No distinction was made in the statute between promotion targeted at physicians vs. consumers, and this Act remains the statutory base guiding the FDA's regulation of promotion to both physicians and consumers. The FDA's 1997 Guidance simply changed the ways in which manufacturers could comply with the requirement to provide a "brief summary" of contraindications etc. in the case of broadcast ads. Previously, the full product label had been required. The 1997 Guidance retained the requirement that ads include a fair balance between risks and benefits but provided that the brief summary could be provided by giving a website, a toll free number, or reference to a print ad, in addition to advice to "see your physician." These changes were deemed to reflect the ways in which consumers currently get information. Given constitutional free speech requirements, the FDA cannot require pre-clearance of ads; however, once they appear the FDA can require changes, removal and even dissemination of corrective information. Promotion of off-label (unapproved) uses of drugs was not permitted until 1993, when companies were permitted to disseminate peer reviewed publications discussing off-label use. In its oversight of promotion, as for its other activities, the FDA is required by statute to consider risks and benefits; costs are not mentioned. Thus the FDA is concerned with the effects of promotion on patients and physicians; whether or not it results in unnecessary costs is beyond its purview.

The pharmaceutical industry's large expenditures on advertising and promotion have been controversial in both the economic literature and the policy debate, with concern over both magnitude and form. The growth of DTC advertising since 1997, in particular, has prompted research to better understand the effects of DTC. The fundamental case for promotion is that it provides information to physicians and consumers about the benefits and risks of drugs, which is necessary for appropriate prescribing and to encourage appropriate patient compliance. Critics question the social value of such large promotional expenditures and charge that they lead to inappropriate use, including use of high-price, on-patent drugs when equally effective generics are available; increased product differentiation, brand loyalty and market power; and higher prices.

3. Evidence on Effects of Pharmaceutical Promotion

Promotion studies pre-1997 An early proponent of the anti-competitive hypothesis, Walker (1971) argues that large promotion expenditures raise entry barriers and increase market power, by requiring new entrants to make large outlays in order to attract attention to new products. The alternative view is that advertising may enhance competition by facilitating the introduction of new products and new firms. Schwartzman (1975) finds that more innovative firms spend larger sums on promotion. Telser (1975) finds that the extent of new entry into a therapeutic class is positively related to promotional intensity. However, it is unclear whether this positive correlation indicates that promotion enhances competitive entry or whether both are simply related to unobservable factors such as technological advance and market potential.

Leffler (1981) estimates a model across therapeutic categories with selling effort as the dependent variable and the number of new products introduced as the primary explanatory variable. He finds a significant positive effect which he interprets as suggesting that pharmaceutical advertising is at least partly informative. He also finds evidence, however, that advertising of established pharmaceutical products accomplishes 'reminder' and 'habit-formation' purposes. These results suggest that the impact of advertising is multidimensional and that the net effect on competition may differ, depending on the circumstances. The distinction drawn by Leffler between the 'persuasion' and 'information' roles of pharmaceutical promotion is extended and supported by Hurwitz and Caves (1988). Berndt et al. (1995) find that promotional stocks of detailing, journal advertising and DTC (pre-1997) significantly affect industry-level demand for anti-ulcerants but with diminishing returns, again suggesting the importance of reminder or loyalty-building promotion.

Beales (1996) uses the FDA policy restricting manufacturer advertising of unapproved indications as a natural experiment to test the importance of pharmaceutical marketing as a source of information for physicians. He analyzes the impact of promotional activity following FDA approval of second indications

for existing drugs on the share of patients treated with the newly approved product, the total fraction of patients treated with drug therapy, and the average price level. He finds some evidence that seller provided information after approval results in increased market share for the new indication as well as lower average price per prescription of other products in the market, suggesting an increase in consumer benefits from increased manufacturer-provided information. However, identifying the impact of FDA approval itself vs. promotional expenditures is problematic.

Effects of DTCA post-1997 Much of the analysis of DTCA has focused on its effects of drug sales, in particular, whether DTCA affects total category sales and/or sales of the individual brand. Although many of these studies use state-of-the-art methods, applied to the best data available and provide valuable evidence, important issues remain unresolved. This reflects both the empirical challenges of measurement and the one hand, and the difficulty of drawing policy conclusions from the results.

One major empirical challenge is that DTCA is endogenously determined and just one of several types of a promotion a firm may use. Ignoring the endogeneity of DTCA and its correlation with other (often unobserved) forms of promotion can potentially lead to serious biases in results. For example, both theory and evidence suggest that promotion is likely to have a higher pay-off for best-in-class drugs. This assumes that physicians, as good agents, are more likely to write the prescription for the best-in-class, even if the patient requests another advertised brand. In that case, an observed positive correlation between promotion and market share may reflect in part these incentives for market leaders to invest more in promotion, leading to upward biased estimates of the reverse effect of promotion on market share. Second, estimating the effects of promotion is further complicated by the fact that information stocks may have long term effects, particularly for chronic medications which patients take indefinitely, once they have found a drug that works for them. Third, the net effect of one firm's promotion depends on similar investments of competitors.

Even with comprehensive data and sound empirical methods, drawing policy conclusions from the empirical evidence on DTCA and promotion remains problematic. The basic difficulty is how to interpret the evidence that promotion increases drug use. The economic/marketing literature generally views advertising that expands aggregate category sales as more likely to be informative, and hence welfare-enhancing, whereas advertising that simply changes market shares without affecting aggregate use is more likely to be wasteful (for a discussion see Berndt, 2005; Kravitz, 2005). However, in the case of heavily insured pharmaceuticals, for which consumers pay only a small fraction of the cost out-of-pocket, it is possible that even category-expanding effects could reflect unnecessary use (and/or unnecessarily costly use), even though such purchases are well-informed and rational for individual consumers.

With these caveats, the main findings from the recent literature are reviewed here (for a more detailed review, see Berndt, 2005). The study of promotional effects in the antihistamine and antiviral

categories by Narayan et al. (2005) is unusual in including data on DTCA, detailing, pricing, and other medical spending as alternative marketing mechanisms to influence sales; measuring both the short and long run effects of promotion; and estimating cross-firm elasticities. All marketing mix variables are modeled as endogenous. This study finds that, of the four marketing variables, only DTCA has a positive but small effect on aggregate category sales. Each product's own DTCA also positively affects its own brand sales, but interaction effects with other brands' DTCA. Own DTCA and detailing appear to be complements, rather than substitutes. The estimated return on investment is lower for DTCA than for detailing, suggesting that firms might gain by reallocating marketing budgets away from DTCA and towards detailing. Although it would be a mistake to generalize the findings of this study, which focused on only two therapeutic categories, it does illustrate the importance of including the full marketing mix and controlling for endogeneity of the marketing variables when estimating the effects of DTCA.

In general, with the important exception of the Narayan et al. (2005) paper cited above, findings from other studies suggest that DTCA has a greater effect on category sales than on individual brand sales. Rosenthal et al. (2003) use data for five large therapeutic categories to estimate effects of DTCA, controlling for sampling and detailing. They conclude that DTCA has a significant positive impact on class sales, with an average elasticity of roughly .1, but they find no evidence that detailing or DTCA has a significant effect on product-specific market shares. The authors emphasize that failure to find brand-specific effects could reflect learning or unmeasured longer term effects. Wosinska (2002) finds that DTCA for the cholesterol reducing medications (statins) positively affects brand share only if the brand had preferred formulary status. Similarly, Iizuka and Jin (2005b) find that DTC A does affect total category sales, but brand-specific share is only significantly shifted by physician promotions such as detailing and journal publications. The authors conclude that drug companies optimally should hold at least 58% market share of their therapeutic market to recoup DTC investment. In fact, 69% of DTC spending is on drugs with at least a 60% market share according to Iizuka and Jin. Another paper by the same authors found that DTCA increases the number of doctor visits at which a drug is prescribed (Iizuka and Jin, 2005a), with few differences between patient types in their responsiveness to DTC (young vs. elderly; private vs. public insurance). Donohue and Berndt (2004) find that DTC has no significant effect on choice of product, but that DTC does motivate individuals to visit the physician.

A randomized control trial by Kravitz et al. (2005) augments the conclusions reached in studies based on observational data on medical claims and DTCA. Standardized patients (who were not sick, but were scripted with dialog to feign depression or adjustment disorder) asked unsuspecting blinded physicians for either A) no medication B) a generic drug or C) a specific brand. For both disorders those who requested were significantly more likely to receive a drug (31% vs 76% vs 53% for depression, 10% vs. 39% vs. 55% for adjustment disorder), but not necessarily the suggested drug (in the case of those who

requested one). Various conclusions can be drawn from these data, including that there is both over and undertreatment of depression, and that responses to patient requests differ across physicians. Policy implications for DTCA regulation are therefore very unclear.

The effects of DTC on quality of care, including compliance with appropriate regimens, are examined by Donohue (2004) and Wosinska (2004). Both study effects of DTCA on patients' adherence behavior. Donohue finds that patients in the top quartile of exposure to DTC had 32% higher odds of initiating therapy (Donohue 2003). Conditional on any therapy, those in the top quartile of DTC spending also had a 30% ($p<.05$) greater probability of adherence (measured as filling at least 4 prescriptions over the first six months of therapy). Wosinska's examination of the Blue Cross and Blue Shield of California data for adherence to statin regimes finds a minor impact for total DTC spending, but current and lagged own DTCA has no affect on product adherence. (Wosinska 2004)

Iizuka (2004) finds that high quality drugs, as defined by whether a drug had "priority" status for FDA approval, have significantly more DTC spending. The interaction term between the quality dummy variable and a dummy variable indicating that the drug was either first or second to market within a particular class also had positive significance. He also finds that DTC spending decisions are significantly related to the potential market size, but not the currently treated market size—a result which supports the notion the DTC has positive social value as it appears to target those in need of medicines rather than those who already take medicines.

4. International Regulation of Promotion

There are no academic studies to our knowledge of international differences in regulation of promotion or its effects. Several countries include in their price regulation systems features that are designed to discourage promotion. The UK PPRS limits the promotional expenditure that can be deducted as a cost in calculating the net rate of return. The provisions of the German global drug budget, that placed the pharmaceutical industry at financial risk for budget overruns (after the share paid by physicians), was intended to discourage promotion. Similarly, the French revenue caps for individual pharmaceutical firms reduce the incentive for promotional effort that would lead to a budget overrun for the firm and hence lower prices.

The only other country that permits DTC product ads, that describe both the product and the condition, is New Zealand. However, DTC in New Zealand is not encumbered by a statute that requires "fair balance" requirement and has a strict freedom of commercial speech commitment. As one might expect, survey results indicate the between 82-90% of individuals recall benefits information in DTC in both the US and New Zealand, but only 20-27% recall risk information in New Zealand compared to 81-89% recall for risks in the US.(Hoek J 2004; Berndt 2005)

5. Promotion to Managed Care

The growth of managed care has fundamentally changed the nature of marketing of pharmaceuticals. The autonomy of the physician has been reduced, with power shifting to payers or their agents, in the form of pharmacy benefit managers or pharmaceutical and therapeutics committees that make formulary decisions, in addition to consumeres. This shift in the primary 'customer' from the physician to a cost-conscious decision maker has been accompanied by a dramatic increase in the importance of cost-effectiveness analysis, to demonstrate that a particular drug is more cost-effective than the alternatives. Use of cost-effectiveness analysis by managed care organizations is summarized in Elixhauser, Luce and Steiner (1995); Newman (2004).

In response to this trend, the FDA proposed regulations that would require that a pharmaceutical firm's cost-effectiveness claims be supported by 'sound' analysis. A debate ensued as to whether this requirement requires a double blind, randomized clinical trial between the two drugs under comparison. Such a requirement would raise the same issues that were debated at the time of the 1962 Amendments: are the gains from reducing the risk of misleading claims outweighed by the costs of additional clinical trials? The social value of head-to-head randomized controlled trials (RCTs) as a requirement for cost-effectiveness claims is weaker than the case for RCTs for efficacy prior to launch. The information on both costs and effects produced from RCTs is not necessarily an accurate measure of cost-effectiveness in actual use, because trials do not mirror actual practice. Moreover, for firms considering investing in such trials, the payoff could be small, especially for trials done after launch, and the risks could be significant, if negative findings must be publicized.

So far the FDA regulations on this issue are vague and certainly do not clearly require RCTs to support economic claims. In fact, the managed care industry has proposed guidelines for studies submitted to its members to support marketing claims ( ). Thus competition is occurring in the provision of cost-effectiveness analyses, including the development of guidelines for the conduct of such studies. But if CMS develops such guidelines for the Medicare Drug Benefit, the private sector may choose to free ride in which case the government guidelines may de facto acquire the status of regulations.

6. Discussion of Promotion

Given the overwhelming evidence that there is both under and overuse of pharmaceuticals, relative to medical guidelines, it is not surprising that finding on the effects of DTCA are mixed. Some of the effects of DTC appear consistent with social welfare, while other evidence suggests some inappropriate effects. Moreover, the policy discussion is less about whether DTCA should be permitted but rather about the appropriate regulatory constraints and enforcement. Such details are too nuanced for empirical analysis.

The recent withdrawals of widely advertised products and of some widely disseminated ads have prompted both the FDA and industry to address their policies related to DTC.(Dubois 2003) Certainly, the staffing levels at the FDA's division of drug advertising, marketing and communications (DDMAC) are overwhelmed with the amount of material they must review, including television and print DTC.(2002) Moreover the HHS policy to review warning letters from the DDMAC since 2001 has further inhibited enforcement.(Gahart, Duhamel et al. 2003) While firms have generally complied with warning letters for infractions and no major disciplinary action has been required, in some instances multiple letters have been sent and the delay in enforcement may have effectively allowed commercials to influence public opinion before modification or withdrawal. Industry has already responded by issuing a set of voluntary guidelines for DTC which reinforce the "fair balance" standard for DTC and stipulate that firms provide copy of DTC advertising prior to, rather than concurrent with, planned public release.(2005) The guidelines also call for greater effort to educate healthcare professionals about products in advance of DTC release.

VIII. Conclusions

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